

ACTG 5056s: METABOLIC STATUS AND CARDIOVASCULAR DISEASE RISK FOR A COHORT OF HIV-1 INFECTED PERSONS DURABLY SUPPRESSED ON AN INDINAVIR CONTAINING REGIMEN (ACTG372A)

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ABSTRACT

Background: CRP levels are a marker of chronic inflammation and have been linked to increased risk for coronary artery disease (CAD). This analysis assessed CRP levels and association of CRP with CAD risk and HIV surrogate marker status in a cohort of HIV-infected patients who achieved durable viral suppression on a regimen that included IDV (ACTG 372A).

Methods: A random sample of 99 ACTG 372A study subjects had CAD risk information obtained along with fasting blood samples. CRP was measured using an ultrasensitive immunonephelometric assay (Dade-Behring, CV=5%).

Results: The median age of the study subjects was 40.5. 32% reported smoking, 14% hypertension, and 10% diabetes. The median time on IDV was 42 months.

The median CRP level (n=99) was 2.29 mg/L (range=0.18-42.9). The distribution of CRP levels by CAD risk categories (for men- **NEJM** 1997; 336:973-9 / for women- **NEJM** 2000; 342: 836-843) was: average risk (<0.55/<1.39mg/L) = 22 subjects ; low risk (0.56-1.14/1.4-2.85 mg/L)= 15 subjects; moderate risk (1.15-2.1/2.86-5.25mg/L)= 13 subjects; and high risk (>2.1/>5.25mg/L)= 49 subjects. The proportion of subjects with high-risk CRP levels was significantly greater than in the general population (p < 0.001). High-risk CRP values were associated with greater age (p = 0.03), fibrinogen levels (p< 0.001), triglyceride levels (p=0.005), HOMA (p = 0.047), WBC (p=0.008), lower HDL levels (p=0.003), lp(a) (p=0.001), and Framingham cardiovascular disease risk scores (p=0.045). High-risk CRP levels were not associated with the baseline, current, or change in CD4+ T-cell levels, or baseline HIV-1 RNA.

Conclusions: In this cohort of durably suppressed HIV-1 infected persons, elevated CRP levels were observed, and tended to cluster with other CAD risk factors. The relationship of this marker of chronic inflammation, in patients with virologically suppressed HIV infection, with long-term CAD risk remains to be defined.

BACKGROUND

There is increasing concern about the health risks associated with the metabolic alterations observed in the setting of treatment for HIV infection. CRP levels are a marker of chronic inflammation that have been shown to be a strong independent predictor of risk for coronary artery disease (CAD) in men (**NEJM** 1997; 336: 973-9) and women (**NEJM** 2000; 342: 836-43). An association between CRP levels and the metabolic syndrome has been described (**Diabetes Care** 2000; 23: 1835-39). Studies have also demonstrated that statin agents (cerivastatin-**Circulation** 2002; 103: 1191-93 and pravastatin-**Circulation** 1999; 100: 230-235) can reduce CRP levels in a lipid-independent manner. Although elevated levels of CRP have been reported in AIDS patients (**J Clin Endocrin Met** 1992; 74:1045-52 and **Am J Physiol** 1999; 276(6 Pt 1):E1092-8) there is no data reported on CRP status in HIV-infected persons on effective treatment and utilizing an ultrasensitive-CRP assay.

OBJECTIVES

This analysis assessed CRP levels and association of CRP with CAD risk and HIV surrogate marker status in a cohort of HIV-1 infected persons who achieved durable suppression in a regimen that included IDV (ACTG 372A).

DESIGN

A random a sample of 99 ACTG 372A study subjects had CAD risk factor information obtained along with fasting blood samples at one study visit. A central laboratory performed measures of fasting glucose, insulin, total/HDL/LDL cholesterol, triglycerides, homocysteine, apo A1, apo B, fibrinogen, and lipoprotein (lp) a. CRP was measured using an ultrasensitive immunonephelometric assay (Dade-Behring, CV= 5%) in the laboratory of one of the investigators (DS). For the analysis of high CRP levels and CAD risk factors, the CRP risk groups slightly increased, moderately increased, and highly increased risk were combined and compared to average-risk CRP data.

STUDY POPULATION

ACTG 372A was a rollover study from ACTG 320 where subjects who were already receiving IDV + ZDV + 3TC with a plasma HIV RNA level < 500 copies/ml were randomized to also receive abacavir or placebo. The median time enrolled in ACTG 372A= 24 months with the total time on IDV= 41.7 months. The median age of the study subjects was 40.5 (13% female, 87% male), 67% were Caucasian, 32% were smokers, 14% had a history of hypertension, and 10% had a personal history of diabetes.

RESULTS

The median CRP level was 2.29 mg/L (range 0.18-42.9). The actual CRP values by sex and age are shown in Figure 1. The distribution of CRP levels by CAD risk categories is shown in Table 1 and depicted graphically in Figure 2.

Table 1- Gender Specific C-reactive Protein CAD Risk Categories for 5056 cohort

	Men (range)	#	Women (range)	#	Total #
Average Risk	< 0.55 mg/L	20	<1.39 mg/L	2	22
Slightly increased	0.56-1.14 mg/L	13	1.4-2.85 mg/L	2	15
Moderately increased	1.15-2.1 mg/L	12	2.86-5.25 mg/L	1	13
High Risk	> 2.1 mg/L	41	> 5.25 mg/L	8	49

The proportion of study subjects with high CRP risk levels was significant (p < 0.001). When all the three categories of increased CRP CAD risk levels were compared to the group with average CRP CAD risk using the Kruskal-Wallis test, the following associations were found: higher risk level CRP values were associated with increased age (p=0.025); higher WBC level (p= 0.008); higher fibrinogen levels (p <0.001); lower HDL levels (p= 0.003); higher triglyceride levels (p= 0.005); higher insulin levels (p=0.037); higher HOMA scores (p= 0.047); and higher Framingham coronary heart disease score (p= 0.057). By the same analysis, non-significant associations were found between higher CRP risk categories and: apo A-1 (p= 0.096); apo B (p= 0.310); total cholesterol (p= 0.366); LDL (p= 0.743); homocysteine (p=0.318); glucose (p=0.804); lp (a) (p= 0.10); and weight (p= 0.252). CRP levels were not associated with the baseline RNA level at entry into ACTG 320.

When the same analysis was used comparing CRP risk level (average or increased) to current CD4+ T-cell count (p= 0.631), pre-therapy baseline CD4+ T-cell count (p= 0.498), or CD4+ T-cell count change (p= 0.066), no significant associations were found.

DISCUSSION

The metabolic syndrome is characterized by insulin resistance accompanied by one or more of the following: abdominal obesity; hypertension; impaired glucose tolerance; low HDL cholesterol levels; and elevated triglyceride levels (≥ 150 mg/dL). There is evidence linking the metabolic syndrome to prothrombotic and proinflammatory states and greatly increased risk of CAD. In this cohort of durably suppressed HIV-1 infected patients, elevated CRP levels were observed and tended to cluster with some features of the metabolic syndrome and other CAD risk factors. Elevated CRP levels were not correlated with CD4+ T-cell factors which would reflect the degree of immune reconstitution. Indinavir has been specifically linked to insulin resistance (**JAIDS** 2001; 27: 130-4 and **AIDS** 2001; 15 : F11-18) and endothelial dysfunction (Dube, **9th CROI 2002; abstract LB-10**) so it is uncertain how generalizable our data would be to populations receiving other potent antiretroviral regimens. More data on CRP levels in varying populations of HIV-1 infected persons is needed. The relationship of this marker of chronic inflammation, in patients with virologically suppressed HIV infection, with long-term CAD risk remains to be defined.

Figure 1- CRP Values by Sex and Age for the 5056 Cohort

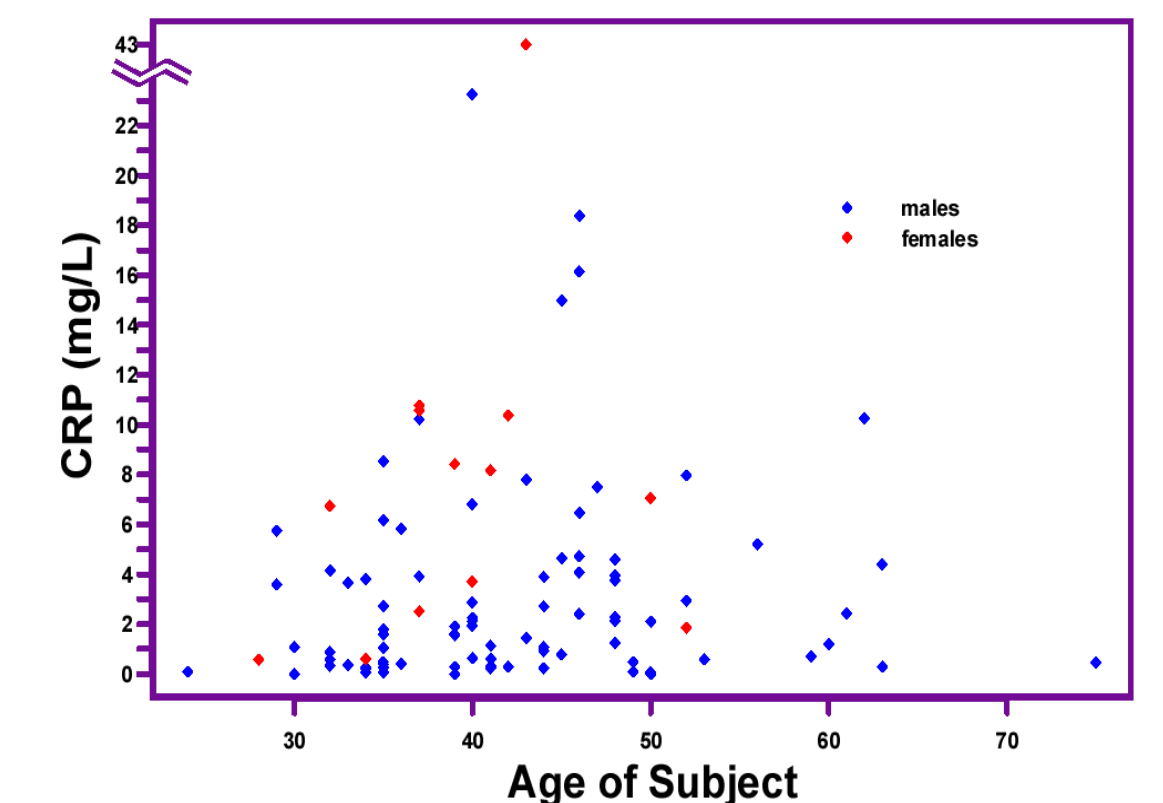


Figure 2- Gender Specific CRP Coronary Disease Risk Categories for 5056 Cohort

